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ALLISON JOHNSON, P.A.
LAKE CALHOUN EXECUTIVE CENTER
3033 EXCELSIOR BLVD., SUITE 467
MINNEAPOLIS, MN 55416

EXAMINER

SHIBUYA, MARK LANCE

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/632,725

Applicant(s)

WOLF ET AL

Examiner

Mark L. Shibuya

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-117 is/are pending in the application.
- 4a) Of the above claim(s) 1-58, 68 and 70-117 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 59-67 and 69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2/5/04; 3/4/04; 3/30/04; 6/09/04
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-117 are pending. Claims 1-58, 68, and 70-117 are withdrawn. Claims 59-67 and 69 are examined.

Election/Restrictions

2. Applicant's election of the Invention of **Group II**, claims 59-69, drawn to a method of assaying for a pathogen in the reply filed on 4/21/2006, is acknowledged. Applicant's election of the species of (a) one probe, (b) antibody, (c) antibody as the species member of a library, (d) fluorescent tag that is a fluorophore, (e) a probe, (f) pathogen, in the reply filed on 4/21/2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Upon further consideration, **Group III**, claims 70-73, drawn to a method of assaying for the presence of a toxin in a sample, is **rejoined** to the elected Invention of Group II.

4. This application contains claims directed to the following patentably distinct species: pathogen component or toxin. The species are independent or distinct because they have materially different modes of operation. Claims 59 and 60 are generic.

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5. As applicant has elected the Invention of methods for identifying pathogens, and in the interest of compact prosecution, the species of pathogen component is considered to have been elected.

6. Claims 1-58 and 74-117 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/21/2006.

7. Claims 68 and 70-73 are withdrawn from further consideration pursuant as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/21/2006.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

9. This application, filed 8/1/2003, claims benefit of U.S. Provisional Application Serial No. 60/461,394, filed Apr. 8, 2003, U.S. Provisional Application Serial No.

60/430,273 filed Dec. 2, 2002, and U.S. Provisional Application Serial No. 60/400,503 filed Aug. 1, 2002.

10. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No.s 60/461,394, filed 4/8/2003 and 60/400,503, filed 8/1/2002, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Provisional Application No.s 60/461,394, filed 4/8/2003 and 60/400,503, filed 8/1/2002, do not provide support for methods of assaying for a pathogen in a sample, comprising antibodies. Therefore, the instant application has an effective filing date of **12/2/2002**, which is the filing date of Provisional Application Serial No. 60/430,273.

Information Disclosure Statement

11. The information disclosure statement (IDS), filed 6/9/2004, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citation to the International Preliminary Examination Report does not provide a publication year. It has

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been placed in the application file, and the writing that is referenced to by the aforementioned citation has been considered; however, the said citation on said IDS has been crossed out. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

12. The information disclosure statements (IDS), filed 2/5/04, 3/4/04, 3/30/04, have been considered.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 59-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the

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steps. See MPEP § 2172.01. The omitted steps are: determining the presence or absence of the pathogen.

Claims 59 and 60 recite the limitation "a sample " in lines 3 and 2, respectively. There is uncertain antecedent basis for this limitation in the claims because it is unclear if this is the same "a sample" in lines 1.

Claim 59 and 60 recite the limitation "a subvolume" in lines 7 and 7, respectively. There is uncertain antecedent basis for this limitation in the claims, because the relationship of "a subvolume" to the "sample" that is excited with radiation, is unclear. That is to say, it is unclear as to whether the "subvolume" is the same as, or different from, the excited "sample".

Applicant's usage of the language of "a predetermined pathogen component" appears to read upon a mental step. It is unclear as to who or what has "predetermined" the pathogen component. Also, it is unclear as to whether the language refers to a mental step or attempts to refer to a structural limitation of the claimed product. It is not disputed that applicant may be their own lexicographer. The examiner does not argue that the term is repugnant to the usual usage in the art. Rather, it is that claim 60 does not reasonably apprise of one skill in the art as to the metes and bounds of the claimed invention.

Claim 63 recites the limitation "said first fluorescent tag" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 69 recites the limitation "a pathogen" twice in line 2. There is uncertain antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 59-67 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Rigler et al., US 6,582,903 B1.

The claims are drawn to a method of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with radiation, said sample comprising at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample; analyzing the fluctuations of said fluorescence; and determining the presence or absence of said pathogen component; and variations thereof.

Rigler et al., throughout the patent, and at col. 16, line 47, teaches detecting pathogens reading on method of assaying for the presence of a pathogen component in a sample; Rigler et al., e.g., at col. 1, lines 55-58, teach fluorescence correlation

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spectroscopy (FCS) using chromophorous molecular structures having fluorescence properties, reading on fluorophores; wherein the fluorophorous molecules in solution are exposed to the intense exciting light of a laser, (Rigler et al. at col. 2, lines 21-24), which reads on exciting a sample with radiation, said sample comprising a complex of a target molecule to be detected and a labeled test reagent, (Rigler et al., at col. 7, lines 14-27), the receptor molecules/ligands, (Rigler et al., col. 8, lines 50-64), including antibodies, which reads further on at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag, (Rigler et al., col. 13, lines 45-62; col. 18, line 41-col. 19, line 2); measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see col. 12, line 62-col. 13, line 10; col. 13, line 62-col. 14, line 45); analyzing the fluctuations of said fluorescence, (Rigler et al., at col. 2, line 7-20); and determining the presence or absence of said pathogen component, (Rigler at col. 8, lines 25-30; col. 16, lines 36-47).

Rigler et al. at col. 2, line 7-31, teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy. In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the examiner respectfully notes that the instant specification states:

Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g.,

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the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Rigler et al., at col. 12, lines-22, teach at least two differently labeled test reagents which will bind to different sequence segments of an analyte, and teach cross correlation of a chromophore 1 and a chromophore 2, (col. 13, line 45-col. 14, line 9), reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Rigler at col. 11, line 45-col. 12, line 22, teaches determining the crosscorrelation function and the autocorrelation function of a sample, reading on claim 64. Rigler at col. 25, lines 10-25, col. 35, lines 57-65, teach pathogens that comprise bacteria or virus, as in claims 65 and 66.

17. Claims 59-64, 66, 67 and 69 rejected under 35 U.S.C. 102(b) as being anticipated by Rigler, Journal of Biotechnology, vol. 41 (1995), pp. 177-186.

Rigler (1995), throughout the publication and abstract, and at pp. 182-184, teach methods of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with laser radiation, (Rigler (1995) at p. 178, Fig. 1), said sample comprising at least one probe (Rigler (1995) at p. 178, para 2) capable of binding a predetermined pathogen component, such as hepatitis B and C or HIV and virus that is M13 bacteriophage, (Rigler (1995) at pp. 182-193, bridging paragraph, and as in claim 65) using several fluorescence labeled primers in the form of a cocktail, (also

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reading on claim 62), reading on methods comprising at least one fluorescent tag, and measuring the fluorescence fluctuations from an extremely small volume element, (Rigler (1995), at p. 177, para 1-2), which reads on a subvolume of said sample and analyzing the fluctuations of said fluorescence, and determining the presence or absence of said pathogen component, (Rigler (1995) at pp. 182-193, bridging paragraph).

Rigler (1995), at p. 182, Fig. 6, teaches cross-correlation in two colors, reading on a plurality of probes with different fluorophore tags, and e.g., at p. 180, teach autocorrelations, as in claims 62-64.

18. Claims 59-61, 66, 67, and 69 rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al., Digestion, 2000, vol. 61, pp. 84-89.

Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen, HCV in a sample, reading on assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with argon-ion laser, radiation, said sample comprising Cy3-labeled amplimers for HCV RNA, (Weiner et al., at p. 85, para 8), reading on a at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample and measuring diffusion times, (p. 85, para 8), reading on

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analyzing the fluctuations of said fluorescence; and determining the presence or absence of said HCV.

19. Claims 59-62, 65, 67, and 69 rejected under 35 U.S.C. 102(b) as being anticipated by Walter et al., Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810.

Walter et al., throughout the publication and abstract and at p.12805, para 1-2, teach a method of assaying for the presence of a *Mycobacterium tuberculosis* pathogen component in a sample, said method comprising: exciting a sample with laser radiation, 9P. 12805, para 1), said sample comprising at least one primer (see Table 1, p. 12807) capable of binding a *M. tuberculosis* DNA pathogen component, and at least one fluorescent rhodamine tag; measuring the fluorescence from a investigated volume (Walter et al. at p. 12805, para 1), reading on a subvolume of said sample; analyzing the fluctuations of said fluorescence, (Walter et al. at p. 12805, para 1); and determining the presence or absence of said pathogen component.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 59-67 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable by **Kask**, US 6,515,289, in view of **Lahiri et al.**, US 2003/0138853 A1.

Kask, US 6,515,289, throughout the patent, and at col. 1, lines 5-13, teaches methods of detecting substances in a sample, said method comprising: exciting a sample with radiation, (Kask at col. 3, line 63-col. 4, line 9), said sample comprising a labeled reactant that binds to a substance, reading on at least one probe capable of binding a predetermined component, and at least one fluorescent tag (col. 8, lines 8-29); Kask at, e.g., col. 2, lines 47-63, teaches monitoring intensity fluctuations of radiation emitted by molecules in a measurement volume, reading on measuring the fluorescence from a subvolume of said sample and analyzing the fluctuations of said fluorescence; and determining the presence or absence of said component, including viruses and bacteria, (col. 6, lines 31-48; and as in claims 65 and 66).

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Kask at col. 1, lines 23-teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy (FCS). In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the instant specification states:

Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Kask, at col. 8, lines 9-50, teaches a plurality of primers labeled with different dyes, reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Kask at, e.g., col. 5, line 65-col. 6, line 3, teach cross-correlation and auto-correlation functions, and combinations thereof, as in claim 64.

Kask et al. do not teach the detection of pathogens.

Lahiri et al., US 2003/0138853 A1, throughout the publication, and at para [0077] teach assay for the presence of a pathogen for diagnosis; and at para [0071], teaches using fluorescence correlation spectroscopy (FCS) as a detection method.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used a method of assaying for the

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presence of a pathogen component in a sample using fluorescence fluctuation methods, such as FCS.

One of ordinary skill in the art would have been motivated to make and use a method of assaying for the presence of a pathogen component in a sample by measuring fluorescence fluctuation, because Lahiri et al. teach using FCS for detecting pathogens for diagnosis and because Kask, at col. 7, lines 37-42, teach using FCS for high throughput screening, and for diagnostic purposes, and teaches the detection of viruses and bacteria, as stated above.

One of ordinary skill in the art would have had a reasonable expectation of success in assaying for the presence of a pathogen by measuring fluorescence fluctuations because Kask et al. teach measuring bacteria and virus by such methods.

Conclusion

22. Claims 59-67 and 69 are rejected.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Mark L. Shibuya
Examiner
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